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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/781,356	02/17/2004	Jian-Qiang Fan	04168/100M413-US1	9219

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EXAMINER	
SCHNIZER, RICHARD A	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 10/04/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/781,356	FAN, JIAN-QIANG	
	Examiner	Art Unit	
	Richard Schnizer, Ph. D.	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 September 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-40* is/are pending in the application.

4a) Of the above claim(s) *6,11-13,21,26-28,33 and 38-40* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,7-9,14-20,22-24,29-32 and 34-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9/11/06 has been entered.

Claims 1-40 are pending.

Claims 6, 11-13, 21, 26-28, 33, and 38-40 were withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to non-elected species.

Claims 1-5, 7-9, 14-20, 22-24, 29-32, and 34-37 and the species of 1-deoxygalactonojirimycin are under consideration in this Office Action.

Drawings

The Application as filed contained no drawings.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-5, 7-9, 14-17, 19, 20, 22-24, 29-32, and 34-37 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Yew et al (US Patent 6,066,626) taken with Fan et al (US Patent 6,274,597).

Yew taught methods of providing biologically active human alpha galactosidase-A to cells of an individual having a deficiency of that enzyme (Fabry's disease) by administration into cells of the individual an adenoviral expression construct encoding alpha galactosidase. See claim 8. The cells may be in vivo (see claims) or ex vivo (see column 9, lines 10-14).

Yew did not teach an active site-specific chaperone.

Fan '597 taught methods of increasing the activity of a mutant form of lysosomal alpha galactosidase-A in mammalian cells, and treating Fabry's disease in an individual, comprising administering an effective amount of 1-deoxygalactonojirimycin. See claims 1-7.

It would have been obvious to one of ordinary skill in the art at the time of the invention to treat an individual with Fabry's disease by administering both the expression construct of Yew, and 1-deoxygalactonojirimycin. One would have been motivated to augment the method of Yew by combining it with the method of Fan above because, in addition to providing the wild type protein of Yew, one would have expected to obtain activity from the patient's endogenous mutant protein as a result of the method of Fan, thereby providing more alpha galactosidase-A activity than would have been obtainable by the separate methods.

Thus the invention as a whole was prima facie obvious.

Claims 1-5, 7-9, 14-17, 19, 20, 22-24, 29-32, and 34-37 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Yew et al (US Patent 6,066,626) taken with and any one of Fan et al (US Patent 6,589,964, issued 7/8/2003), Fan et al (US Patent 6,599,919 issued 7/29/2003), or Fan et al (US Patent 6,774,135, issued 8/10/2004).

The applied references Fan et al (US Patent 6,589,964, issued 7/8/2003), Fan et al (US Patent 6,599,919 issued 7/29/2003), and Fan et al (US Patent 6,774,135, issued 8/10/2004) have a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, they constitute prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). This rejection might also be overcome by showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2).

Yew taught methods of providing biologically active human alpha galactosidase-A to cells of an individual having a deficiency of that enzyme (Fabry's disease) by administration into cells of the individual an adenoviral expression construct encoding alpha galactosidase. See claim 8. The cells may be in vivo (see claims) or ex vivo (see column 9, lines 10-14).

Yew did not teach an active site-specific chaperone.

Fan '964 taught methods of enhancing in a mammalian cell the activity of an enzyme, which method comprises administering a competitive inhibitor of the enzyme in an amount effective to enhance enzyme activity. See claim 1. Fan also taught methods of increasing the activity of a mutant form of lysosomal alpha galactosidase-A in mammalian cells, and treating Fabry's disease in an individual, comprising administering an effective amount of 1-deoxygalactonojirimycin. See e.g. claims 1-10, and 41-47, especially claims 9, 10 and 47.

Fan '919 taught methods of enhancing in a mammalian cell the activity of an enzyme, which enzyme when mutated tends to fold in an incorrect conformation in endoplasmic reticulum (ER), and whereby a level of the active enzyme is deficient as a result of such mutation, which method comprises administering a competitive inhibitor of the enzyme in an amount effective to enhance enzyme activity. Fan also taught such a method wherein the competitive inhibitor is 1-deoxygalactonojirimycin. Fan also taught methods of treating a glycosphingolipid storage disease by administering 1-deoxygalactonojirimycin. See claims 1-16, and 18-42, especially claims 18 and 19.

Fan '135 taught methods of treating Fabry's disease comprising administering to an individual in need thereof an effective amount of 1-deoxygalactonojirimycin. See claims 1, 3, 4, 7, 9, 10, 12, 13, 15-17, 21, 23-25, 29, and 31-36.

It would have been obvious to one of ordinary skill in the art at the time of the invention to treat an individual with Fabry's disease by administering both the expression construct of Yew, and 1-deoxygalactonojirimycin. One would have been motivated to augment the method of Yew by combining with any of the methods of Fan above because, in addition to providing the wild type protein of Yew, one would have expected to obtain activity from the patient's endogenous mutant protein as a result of the methods of Fan, thereby providing more alpha galactosidase-A activity than would have been obtainable by the separate methods.

Thus the invention as a whole was prima facie obvious.

Claims 17 and 18 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Yew et al (US Patent 6,066,626) taken with Fan et al (US Patent 6,274,597) as applied to claims 1-5, 7-9, 14-17, 19, 20, 22-24, 29-32, and 34-37 above, and further in view of Hendricks et al (Blood 96 (11 part 1): 845a, 2000).

The teachings of Yew and Fan are discussed above, and can be combined to render obvious methods of increasing the level of expression of alpha galactosidase in an individual by administering to the individual cells comprising an alpha galactosidase expression vector and 1-deoxygalactonojirimycin.

Yew and Fan did not teach administration of human primary cells or mesenchymal stem cells comprising an alpha galactosidase expression vector.

Hendricks taught a method in which human mesenchymal stem cells were transduced with a retroviral expression vector encoding alpha galactosidase A, and then were implanted into mice where they secreted high levels of alpha galactosidase A suggesting their usefulness as gene delivery vehicles for the treatment of Fabry's disease. See abstract.

It would have been obvious to one of ordinary skill in the art at the time of the invention to administer human mesenchymal stem cells comprising an alpha galactosidase A expression vector to a human individual for the purpose of increasing the expression level of alpha galactosidase A in the individual. One would have been motivated to do so because Hendricks suggests that human mesenchymal stem cells transduced to express alpha galactosidase A would be useful as gene delivery vehicles for the treatment of Fabry's disease.

Thus the invention as a whole was prima facie obvious.

Claims 17 and 18 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Yew et al (US Patent 6,066,626) taken with any one of Fan et al (US Patent 6,589,964, issued 7/8/2003), Fan et al (US Patent 6,599,919 issued 7/29/2003), or Fan et al (US Patent 6,774,135, issued 8/10/2004) as applied to claims 1-5, 7-10, 14-17, 19, 20, 22-24, 29-32, and 34-37 above, and further in view of Hendricks et al (Blood 96 (11 part 1): 845a, 2000).

The teachings of Yew and Fan '964, '919, and '135 are discussed above and can be combined to render obvious methods of increasing the level of expression of alpha galactosidase in an individual by administering to the individual cells comprising an alpha galactosidase expression vector and 1-deoxygalactonojirimycin.

Yew and Fan did not teach administration of human primary cells or mesenchymal stem cells comprising an alpha galactosidase expression vector.

Hendricks taught a method in which human mesenchymal stem cells were transduced with a retroviral expression vector encoding alpha galactosidase A, and then were implanted into mice where they secreted high levels of alpha galactosidase A suggesting their usefulness as gene delivery vehicles for the treatment of Fabry's disease.

It would have been obvious to one of ordinary skill in the art at the time of the invention to administer human mesenchymal stem cells comprising an alpha galactosidase A expression vector to a human individual for the purpose of increasing the expression level of alpha galactosidase A in the individual. One would have been motivated to do so because Hendricks suggests that human mesenchymal stem cells transduced to express alpha galactosidase A would be useful as gene delivery vehicles for the treatment of Fabry's disease.

Thus the invention as a whole was prima facie obvious.

Response to Arguments

Applicant's arguments filed 9/11/06 have been fully considered but they are not persuasive.

Applicant addresses the obviousness rejections at pages 9-16 of the response.

At page 12, Applicant argues that one of skill in the art would not be motivated to combine the gene therapy and chaperone methods because chaperone therapy would achieve sufficient levels of protein activity such that gene therapy would be unwarranted. For support, Applicant refers to the '597 patent and its teaching of 2- to 5-fold increases in activity in mutant mice and concludes that this improvement corresponds to an activity level that is greater than 10-30% of the activity generally seen in humans, noting that 10-30% of human wild type activity is thought to be sufficient to either prevent the major clinical manifestations of the disease (Desnick , 2001, p3749), or to significantly improve symptoms in Fabry patients (column 3, lines 45-52 of '597). However, Applicant fails to disclose what was the original activity level in the mutant mice, expressed as a percent of wild type. As a result one cannot draw the conclusion that a 2- to 5-fold increase in activity in mutant mice corresponds to an activity level that is greater than 10-30% of the activity generally seen in humans. If the activity level in untreated mice was 1% of wild type, then treated mice showed no better than 5% activity. Furthermore, Applicant presented no evidence to suggest that one could reasonably expect to get a 2- to 5-fold increase in activity regardless of the activity level of the patient. One of skill in the art appreciates that different alpha galactosidase A misfolding mutations might show different levels of amenity to chaperone treatment.

Some mutations might have an equilibrium constant favoring the inactive enzyme form that is greater than that of other mutations. One would reasonably expect chaperone therapy to be less successful in these cases. Applicant has provided no evidence that chaperone therapy provides sufficient results to completely alleviate disease symptoms in all patients in which it can be performed.

Applicant argues in the paragraph bridging pages 12 and 13 that there would be no reason to augment gene therapy with chaperone therapy because Yew showed that high dose adenoviral gene therapy provided much higher than wild type levels of alpha galactosidase A. This is unpersuasive for several reasons. First, it is totally unpredictable as to whether or not one of skill in the art could obtain similar expression levels in humans as were obtained in mice. Second, it should be noted that low dose adenovirus therapy gave less than wild-type levels (see Fig. 9). As a result one of skill in the art could take advantage of chaperone therapy to augment adenoviral gene therapy while using a lower, safer, less immunologically potent dose of adenovirus. Third, those of skill in the art recognize that adenoviral gene delivery generally allows for much greater expression levels than safer, non-viral means. It follows that such safer, non-viral means could be combined with chaperone therapy to treat Fabry disease, as stated in the rejections.

Applicant also argues that the combination of the two therapies is invasive and cost prohibitive. This is unpersuasive because decisions as to what level of invasiveness and cost are appropriate are made on a case by case basis. Applicant

has presented no evidence to support the idea that invasiveness and cost of combining the two therapies would be prohibitive or render the combination non-obvious.

Applicant indicates at page 13 that the rejection seems to presume that every patient who is treated using gene therapy expresses a form of the protein that is amendable to chaperone therapy, and states that the Examiner presumes that every patient who endogenously expresses some portion of a deficient protein would benefit from chaperone therapy. This is false. The rejection cites prior art directed to two different, non-mutually exclusive treatments of Fabry disease. One of skill in the art understands that chaperone therapy is only applicable to situations in which a mutant protein can be refolded and would act accordingly. The fact that some forms of Fabry disease cannot be treated by chaperone therapy does not in any way mean that it would not be obvious use the method when it is appropriate, or to combine it with gene therapy in order to obtain the benefits of both approaches simultaneously. Finally, to the extent that Applicant argues that it would not be obvious to combine the treatments in cases where chaperone therapy is inapplicable, Applicant is arguing limitations that are not in the claims. The claims are not limited to situations that require gene replacement therapy, i.e. situations in which the patient has a mutation that does not allow refolding of an active protein through binding of a chaperone

For these reasons the rejections are maintained.

Conclusion

No claim is allowed.

This is a request for continued examination of applicant's earlier Application No. 10/781,356. All claims are drawn to the same invention claimed in the earlier application and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the earlier application. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action in this case. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no, however, event will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:00 AM and 3:30 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Peter Paras, can be reached at (571) 272-4517. The official central fax

number is 571-273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Richard Schnizer, Ph.D.
Primary Examiner
Art Unit 1635